EXHIBIT C

8

Glycopeptide Pharmacodynamics

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1 INTRODUCTION

Pharmacodynamics represents a blending of pharmacokinetic parameters with a measure of bacterial susceptibility, the minimum inhibiting concentration (MIC). As such, there is a prerequisite that the pharmacokinetic parameters of the antibiotic be adequately defined prior to exploring the drug's pharmacodynamic properties. This in itself has not been an easy task with a drug such as vancomycin, which has undergone several different formulation changes to remove impurities and increase the drug's purity.

Measuring vancomycin concentrations by any method other than microbiological assay was not possible until the late 1970s when a radioimmunoassay was introduced. Microbiological assays were technically challenging, were accurate at best to ±10% [1], and often could not be performed if patients were receiving other antibiotics.

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Pharmacokinetically, vancomycin, the only commercially available glycopeptide in the United States, has been characterized using one-, two-, and three-compartment models as well as noncompartmentally. As a result, there is model-dependent variability in the reporting of vancomycin pharmacokinetic parameters. Thus, getting to a point where clinically applicable pharmacodynamic parameters could be identified and quantified has not been easy. Even today, there are extremely limited in vitro, animal, and human data characterizing vancomycin's performance against only a few bacteria. Clearly, the characterization and quantification of vancomycin pharmacodynamics remains a work in progress. The purpose of this review is to examine the microbiology, pharmacology, and pharmacokinetics of vancomycin so as to build on the data presently available for describing the pharmacodynamics of the drug.

1.1 History of Vancomycin

Vancomycin was first introduced in 1956, with widespread clinical use by 1958 [2]. Originally, the drug was isolated from the actinomycete *Streptomyces orientalis*; however, its structure and molecular weight were not identified until 1978. The compound consists of a seven-membered peptide chain and two chlorinated β-hydroxytyrosine moieties with a molecular weight of 1449 [2]. Clinical use of the drug was highly prevalent in the late 1950s due to the emergence of penicillinase-producing strains of staphylococcus, but it soon lost favor with the introduction of methicillin. Impurities in early vancomycin formulations led to an unacceptable incidence of infusion-related reactions. Subsequently, for 20 years, vancomycin was used exclusively for the treatment of serious staphylococcal infections in patients with severe penicillin allergies. The current Eli Lilly formulation, marketed in 1986, is estimated to be 93% pure factor B (vancomycin) and is the result of several production changes and improved separation techniques [2]. With the enhancement in purity and the heightened frequency of methicillin-resistant staphylococci and ampicillin-resistant enterococci, clinical use of vancomycin has significantly increased. Today, approximately 800,000 patients receive vancomycin each year, accounting for 14,000 kg of drug worldwide [3].

1.2 Antimicrobial Spectrum

Vancomycin is primarily effective against gram-positive cocci, including staphylococcus, streptococcus, and enterococcus, and is considered to be bactericidal (MBC/MIC ≤ 4) against most gram-positive pathogens with the exception to enterococci, limited numbers of tolerant (MBC/MIC > 32) *S. pneumoniae*, and tolerant staphylococci. The National Committee for Clinical Laboratory Standards has established minimum inhibitory concentration (MIC) standards of susceptibility for vancomycin against staphylococci and enterococci [4]. Sensitive strains have MICs of ≤4 mg/L, intermediate isolates have MICs of 8–16 mg/L, and resistant strains have MICs >32 mg/L. *Staphylococcus aureus* and *Staphylococcus epidermidis*, including both methicillin-susceptible and methicillin-resistant strains, are usually sensitive with MIC_{90} values of ≤2 mg/L [5]. All strains of *Streptococcus* are sensitive to vancomycin, regardless of penicillin susceptibility, with MIC_{90} values less than 1 mg/L [4]. A recent report, however, claims that approximately 2% of *S. pneumoniae* isolates have developed tolerance to vancomycin [6]. *Enterococcus faecalis* organisms are typically susceptible to vancomycin with MIC_{90} ≤1 mg/L, whereas *Enterococcus faecium* are generally nonsusceptible with MIC_{90} ≥16 mg/L [5]. Vancomycin is also effective against other Streptococcus spp., *Listeria monocytogenes*, *Bacillus* spp., Corynebacteria, and anaerobes such as diphtheroids and *Clostridium* spp., including *C. perfringens* and *C. difficile*. Vancomycin has no activity against gram-negative organisms, atypical pathogens, fungi, or viruses.

2 PHARMACOLOGY

Vancomycin has multiple mechanisms of action: preventing the synthesis and assembly of a growing bacterial cell wall, altering the permeability of the bacterial cytoplasmic membrane, and selectively inhibiting bacterial RNA synthesis [7]. Vancomycin prevents polymerization of the phosphodisaccharide–pentapeptide–lipid complex of the growing cell wall at the D-alanyl-D-alanine end of the peptidoglycan precursor during the latter portion of biosynthesis [7–8]. By tightly binding the free carboxyl end of the cross-linking peptide, vancomycin sterically prevents binding to the enzyme peptidoglycan synthetase. This activity occurs at an earlier point and at a separate site from that of penicillins and cephalosporins [8]. Therefore, no cross resistance or competition of binding sites occurs between the classes. Vancomycin, like β-lactams, does require actively growing bacteria in order to exert its bactericidal effect. However, vancomycin's bactericidal activity is restricted to gram-positive organisms because the molecule is too large to cross the outer cell membrane of gram-negative species.

Many factors appear to impede vancomycin's bactericidal activity: the absence of environmental oxygen, the size of the bacterial inoculum, and the phase of bacterial growth. The antibiotic appears to kill bacteria more effectively under aerobic conditions than under anaerobic conditions [9]. The fact that many gram-positive pathogens, including streptococcus and staphylococcus, can grow under aerobic and anaerobic conditions could prove problematic in clinical situations. Vancomycin activity was reduced by 19% and 99% with increases in inoculum size from 10^6 CFU/mL to 10^7 and 10^8 CFU/mL, respectively [10–11]. When vancomycin was evaluated against growing and nongrowing *Staphylococcus epidermidis* cells, the drug was found to be effective only against actively growing cultures [12]. Finally, activity is relatively unaffected by extremes in pH but is maximal at pH 6.5–8.0 [10,11,13].

3 PHARMACOKINETICS

The pharmacokinetics of vancomycin are highly dependent upon the modeling method used to characterize the parameters. Data can be found in the literature that characterize vancomycin using one-, two-, three-compartment and noncompartmental pharmacokinetic models that employ different serum sampling schemes and vary in the duration of study. As a result the literature varies in the reporting of vancomycin pharmacokinetic parameters.

Absorption is complete only when the drug is given intravenously, because oral absorption is poor and intramuscular administration is both erratic and painful. Vancomycin is readily absorbed after intraperitoneal administration also [14].

The distribution of vancomycin is a complex process and is best characterized by using a multicompartmental approach. Vancomycin has a large volume of distribution, varying from 0.4 to 0.6 L/kg in patients with normal renal function and up to 0.9 L/kg in patients with end stage renal disease [13,15,16]. Distribution includes ascitic, pericardial, synovial, and pleural fluids as well as bone and kidney. Penetration into bile, however, is generally considered poor. Cerebral spinal fluid concentrations are minimal unless sufficient inflammation is present where 10–15% of serum concentrations can be obtained [13,15]. Approximately 10–50% of vancomycin is protein-bound, primarily to albumin, providing a relatively high free fraction of active drug [13,17]. Studies attempting to measure the effect of other serum proteins have reported virtually no binding to the reactive protein, α-1 glycoprotein, but have noted binding to IgA [17].

Drug elimination is almost exclusively via glomerular filtration, with 80–90% of the vancomycin dose appearing unchanged in the urine within 24 h in patients with normal renal function [13,15,16]. The remainder of the dose is eliminated via biliary and hepatic means. Vancomycin, when taken orally, is excreted primarily in the feces. Vancomycin is not significantly removed by conventional hemodialysis or peritoneal dialysis owing to its large molecular weight (~2000), however, high-flux dialyzers can remove vancomycin and other molecules with molecular weights of less than 20,000 [18].

The elimination of vancomycin is multicompartmental, with an alpha, or distribution, half-life of 0.6–3 h and a beta, or elimination, half-life of 4–8 h with normal renal function [15,16]. Renal insufficiency can prolong the terminal half-life to as much as 7–12 days. Due to the complexity of this biexponential decay, attempts to utilize various modeling techniques are difficult. A one-compartment model inappropriately characterizes the distribution phase by formulating a regression line that is a hybrid of the alpha and beta phases. The pharmacokinetic parameters produced are accordingly mythical values that may or may not relate to the actual parameters. The extrapolated peak concentration and the half-life can be greatly underestimated depending upon the sampling scheme used. Generally, pairing a serum concentration obtained early in the distribution phase

with a serum concentration late in the elimination phase results in the greatest error. Because one compartment modeling also underestimates the area under the serum concentration–time curve, this error is passed along in the calculation of both distribution volume and drug clearance.

For a concentration-independent or time-dependent antibiotic, vancomycin has an almost ideal pharmacokinetic profile. The drug has a large volume of distribution, low serum protein binding, and a long terminal half-life. Additionally, due to modest hepatic metabolism, vancomycin-drug interactions are limited. As such, vancomycin can be used effectively and conveniently to treat infections in most body sites.

4 GLYCOPEPTIDE RESISTANCE

Vancomycin has been in clinical use for over 40 years without the emergence of resistance. The multiple modes of action of vancomycin necessitate significant alterations in bacterial wall synthesis in order for the intrinsically susceptible organisms to develop resistance. Thus, the rarity of acquired vancomycin resistance led to predictions that such resistance is unlikely to occur on any significant scale [19,20].

The first reports of vancomycin-resistant enterococci, however, began to appear in Europe in the mid-1980s [19]. How the enterococci were able to develop resistance to vancomycin is unclear. However, several hypotheses have been elucidated, ranging from the overuse of antibiotics to the incorporation of glycopeptide antibiotics into animal feed.

Enterococci are normal gut flora, and the emergence of resistance has been linked to vancomycin overuse in the treatment of *Clostridium difficile* enterocolitis [20]. Additionally, the parenteral use of vancomycin has steadily increased since the late 1970s and may have played a role in the development of vancomycin-resistant enterococci (VRE) [21]. The agricultural use of avoparcin, a related glycopeptide, may have been important in Europe, but this drug has not been used in the United States. In any case, the enterococci were the first class of organisms to acquire vancomycin resistance, and vancomycin resistance are now problematic in both Europe and the United States [20].

The genetic basis for glycopeptide resistance in enterococci is complex and is characterized by several different phenotypes. Resistance-conferring genes encode a group of enzymes that enable the enterococci to synthesize cell wall precursors generally ending in D-alanine-D-lactate rather than the usual D-alanine D-alanine vancomycin binding site [22–23]. The affinity of vancomycin and teicoplanin for D-alanine-D-lactate is 1,000-fold less than that for D-alanine-D-alanine [20].

The most frequently encountered resistance phenotype, *vanA*, consists of high level vancomycin resistance (MIC ≥ 32 mg/L) accompanied by high level

resistance to teicoplanin [22]. The resistance found on *vanA* strains is vancomycin- and/or teicoplanin-inducible. The genes encoding *vanA* resistance are relatively easily transferred to other enterococcal species via conjugation [22,23]. Significant concern has been expressed in both the lay and professional literature that this plasmid mediated form of resistance could be passed on not only to other enterococci but also to gram-positive organisms, such as staphylococci, which could lead to catastrophic consequences worldwide. Although this event has not been realized naturally, the *vanA* plasmid has been successfully introduced into staphylococci in the laboratory, raising concerns that given enough time vancomycin-resistant staphylococci will eventually become a clinical problem [24].

Enterococci with *vanB* phenotypic resistance have variable levels of vancomycin resistance and are susceptible to teicoplanin. The *vanB* phenotype is inducible by vancomycin but not teicoplanin, and vancomycin exposure produces teicoplanin resistance. Genes that encode *VanB* are more commonly chromosomal but can be transferred by conjugation [22,25].

The *vanC* resistance phenotype consists of relatively low levels of vancomycin resistance (MIC = 8–16 mg/L) and is devoid of teicoplanin resistance. Resistance to *vanC* is chromosomally produced by encoded genes found in all strains of *Enterococcus flavescens*, *Enterococcus casseliflavus*, and *Enterococcus gallinarum*. Genes encoded with *vanC* are not transferable [20]. In 1996 Perichon et al. [26] described a fourth phenotype, *vanD*, similar to *vanB*, found in a rare strain of *Enterococcus faecium* [26].

Following a steady increase of VRE prevalence in the United States over the past 10 years, almost 15% of enterococci in hospital intensive care units (participating in the National Nosocomial Infections Surveillance surveys) exhibit vancomycin resistance [23,27]. Similarly rapid increases in VRE prevalence have also been observed outside the intensive care units in U.S. hospitals [23]. Approximately 70% of VRE found in the United States exhibit the *vanA* resistance phenotype with the remaining 25% mostly constituted by the *vanB* resistance phenotype [28].

Evidence exists for both clonal dissemination of resistant strains and rapid transfer of vancomycin resistance genes among species of hospital enterococci [29–30]. With the transfer of resistance genes, multiple different enterococcal subtypes carry the same vancomycin resistance genes, suggesting a possible "plasmid or transposon VRE epidemic" [20]. Considerable heterogeneity in the genetic sequence of vancomycin resistance genes found in the United States further suggest that these genes are being modified as they spread among the various enterococcal strains [31].

The greatest threat VRE pose is the potential that they could transfer their resistance encoding genes to other more pathogenic gram-positive bacteria. Vancomycin resistance has been transferred from enterococci to streptococci, listeria,

and *S. aureus* in vitro [24,32]. Also, the recent description of a naturally occurring vancomycin-resistant strain of *Streptococcus bovis* harboring the *vanB* resistance phenotype is of significant concern [33].

Low-level vancomycin resistance was reported in clinical isolates of coagulase-negative staphylococci in the late 1980s and early 1990s [34–36]. Although troubling, these reports were not terribly feared due to the relative lack of virulence associated with the coagulase-negative staphylococci. In vitro studies, however, demonstrated that both coagulase-negative staphylococci and *S. aureus* isolates, when exposed to increasing levels of glycopeptides, demonstrated the ability to select for resistant subpopulations [37,38]. Given these findings and the spread of VRE, for which excessive use of vancomycin was identified as an important control measure, the prudent use of vancomycin was suggested by the CDC as critical to prevent the emergence of resistance among staphylococci [39].

In May 1996 a methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolate that had reduced susceptibility to vancomycin (MIC = 8 mg/L) was isolated from a 4 month-old boy with a sternal surgical incision site [40,41]. This isolate has been referred to as Mu50 by the investigators who isolated the organism. By current NCCLS standards, this *S. aureus* clinical isolate is classified as having intermediate resistance to vancomycin. In August 1997, the first MRSA isolate intermediately susceptible to vancomycin was reported in Michigan and New Jersey [42,43]. Since these reports, the organism has been identified in New York and England. The two U.S. isolates exhibited different antimicrobial susceptibility patterns, suggesting that these strains are developing de novo secondary to vancomycin exposure. All of these decreased susceptibility strains were isolated from patients who had received multiple extended courses of vancomycin therapy.

The exact mechanism of resistance for these glycopeptide intermediate susceptibility *S. aureus* (GISA) strains remains largely unknown. None of the GISA strains isolated to date have carried the *vanA* or *vanB* genes as judged by PCR DNA amplification. Changes in the GISA cell wall structure have been noted, however, and may be in part responsible for the decreased sensitivity to vancomycin. This is inferred from three findings: The cell wall appeared twice as thick as the wall of control strains on electron microscopy; there was a three fold increase in cell wall murein precursor production compared with vancomycin-susceptible MRSA strains; and there was a threefold increase in the production of penicillin-binding protein (PBP) 2 and PBP2′ [40,41].

To date, there is no evidence that vancomycin resistance genes have been naturally transferred to the staphylococci or pneumococci, however, that does not preclude this event from happening in the future. If such a transfer of vancomycin resistance were to occur, particularly if the *S. aureus* strain is already methicillin-resistant, the result would be an especially terrifying pathogen.

5 PHARMACODYNAMICS

5.1 Introduction to Basic Principles

Evaluations of serum peak/MIC ratios, the ratio of the area under the serum concentration–time curve for 24 h to the MIC (AUC/MIC_{24}), and the length of time for which antibiotic concentration exceeds the MIC of the infecting organism ($T > MIC$) have been employed as surrogate markers of the bactericidal effects of antibiotics. Pharmacodynamic indices for vancomycin have been poorly characterized, and therefore most dosing strategies have been based on extrapolations from aminoglycoside studies. By modifying aminoglycoside dosing models, specific peak and trough concentrations have been proposed with the assumption that similar clinical outcomes will be produced, high peak concentrations being essential for bacterial killing and definitive trough concentration ranges minimizing drug-related toxicity.

On the basis of limited in vitro studies, $T > MIC$ appears to most closely predict efficacy of vancomycin. Therefore, the length of time the antibiotic concentration exceeds the MIC of the offending organism and not the height of the peak above the MIC, as in aminoglycosides, should be considered the goal of the dosing of vancomycin. Although higher serum concentrations of vancomycin may be helpful in driving the drug to relatively inaccessible sites of infection such as endocardial vegetation or cerebrospinal fluid, they are unlikely to improve the rate of bacterial kill. Attempting to push the dose of vancomycin for serious but relatively accessible infections will likely only expose patients to an increased risk of adverse reactions; it is unlikely this approach will alter bacterial response.

Investigations of other pharmacodynamic parameters, including postantibiotic effect (PAE), sub-MIC effect (SME), and postantibiotic sub-MIC effect (PA SME), have also been undertaken to create a more informative depiction of vancomycin bactericidal activity than MICs allow alone. The PAE, or the continued suppression of microbial growth after limited antibiotic exposure of vancomycin against gram-positive bacteria, can persist for several hours depending on the organism and the initial antibiotic concentration [44,45]. This effect may inhibit regrowth when antibiotic concentrations fall below the MIC of the infecting organism, and may be important to consider when dosing vancomycin because of the extended half-life and prolonged dosing intervals. The postantibiotic effect of vancomycin was evaluated against *Staphylococcus epidermidis* by Svensson et al. [12]. The PAE was dependent upon concentration, as drug concentration increased from 0.5 to 8 times the MIC of the organism, the PAE increased from 0.2 h to 1.9 h. Another study found PAEs ranging from 0.6–2.0 h for *S. aureus* to 4.3–6.5 h for *S. epidermidis* [46].

Because patients receiving antibiotics will always have some amount of drug remaining in the body after dosing and elimination, PAEs are typically studied in vitro. SMEs and PA SMEs are parameters studied in vivo. Generally all of these effects are longer when measured in vivo than when measured in vitro. SMEs characterize the inhibition of bacterial regrowth following initial sub-MIC concentrations of antibiotic [46]. Postantibiotic SMEs, on the other hand, illustrate microbial suppression following bacterial exposure to supra-MIC concentrations that have declined below the MIC. This phenomenon is important clinically where patients given intermittent boluses will experience gradually lowered serum and tissue levels that will expose bacteria to both supra- and sub-MICs during the dosing interval [46].

5.2 In Vitro Studies

In vitro investigations have demonstrated that, like β-lactam antibiotics, vancomycin is a concentration-independent or time-dependent killer of gram-positive organisms and exhibits minimal concentration-dependent killing. In vitro studies, however, can be limiting for several reasons [47]:

1. One compartment models represent only concentrations that would exist in the central compartment and not necessarily those that would exist at the site of infection.
2. Typically only bacteria in log phase growth at standard inocula (10^5 or 10^6 CFU/mL) are used.
3. The effects of the immune system or protein binding are generally not considered.

Despite the limitations, in vitro studies appear to correlate well with animal and human studies and therefore provide useful information for optimal dosing strategies in clinical situations.

Several investigators demonstrated the concentration-independent killing of vancomycin by exposing various bacteria to increasing amounts of the drug. Vancomycin's killing effect against *Staphylococcus aureus* was investigated in vitro by Flandrois et al. [48]. The early portion of the time–kill curve was the focus of the study to characterize the bactericidal activity in the initial phases of the dosing interval. A decrease in CFU of only 1 log was obtained at the end of the 8 h study at concentrations of 1, 2.5, 5, and 10 times the MIC, indicating a concentration-independent, slow rate of kill. The killing phase occurred between hours 2 and 4, with the CFU/mL being held constant for the remainder of the curve. Ackerman et al. generated mono- and biexponential killing curves for vancomycin over a 2–50 μg/mL concentration range to evaluate the relationship between concentration and pharmacodynamic response against *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species. For all organisms tested,

of vancomycin significantly reduced bacterial counts to a greater extent than any other combination regimen. Whether this finding is due to augmented penetration into the fibrin clots in the presence of gentamicin is unknown.

The vast majority of pharmacodynamic investigations with vancomycin include the use of *Staphylococcus aureus*, few studies involve other gram-positive or anaerobic organisms. Lovett [52] demonstrated time-dependent killing of *Clostridium difficile* by vancomycin in vitro. Vancomycin was sub inhibitory at concentrations below the MIC of the organism. Once concentrations at the MIC were obtained, no difference in kill was seen whether 4 mg/L (at the MIC) or 1000 mg/L (250 × MIC) was utilized. Therefore, as for other organisms, vancomycin kills *C. difficile* in a concentration-dependent manner until the MIC is achieved, beyond which time-dependent killing is observed.

Odenholt-Tornqvist, Lowdin, and Cars have been the primary source of investigations on the SMEs and PA SMEs of vancomycin. In an initial study with *Streptococcus pyogenes* and *Streptococcus pneumoniae*, the investigators found that the PA SME with concentrations as low as 0.3 × the MIC prevented regrowth of both Streptococcus species for 24 h [53]. In a recent in vitro investigation of the pharmacodynamic properties of vancomycin against *Staphylococcus aureus* and *Staphylococcus epidermidis*, the same authors detected no concentration-dependent killing [46]. Low killing rates were demonstrated by time to 3 log kill (T3K) at 24 h with all strains, the exception being a methicillin-sensitive strain of *Staphylococcus epidermidis* (MSSE) that attained T3K at 9 h. Regrowth occurred between 12 and 24 h when drug concentration had declined to the MIC. PA SME, SME, and post-MIC effect (PME) were also evaluated in this study. Long PA-SMEs (2.3 to ≫20 h) were found with all strains while SMEs were shorter (0.0–15.8 h). Both PA-SMEs and SMEs increased with increasing multiples of the MIC. Interestingly, longer PMEs, "the difference in time for the numbers of CFU to increase 1 log/mL from the values obtained at the time when the antibiotic concentration has declined to the MIC compared with the corresponding time for a antibiotic-free growth control" [46], were found with shorter half-lives. Other investigations have suggested that the regrowth of bacteria can occur if insufficiently inhibited bacteria are allowed to synthesize new peptidoglycan to overcome the antimicrobial's bactericidal effect [54]. The authors assumed that the PAE, PA SME, and PME would emulate the time for which the amount of peptidoglycan is kept below a critical level needed for bacterial growth [46]. Subsequently, the investigators postulated that longer PMEs may occur with shorter half-lives due to the fact that the MIC is obtained faster, thereby not allowing adequate peptidoglycan production to initiate regrowth. Conversely, shorter PMEs were found with longer half-lives. With a slower decline to the MIC and a longer period of time at the MIC, sufficient peptidoglycan could be produced to allow regrowth. How PA-SMEs, SMEs, and PMEs will influence dosing schedules is unknown and further investigations are needed.

killing rates did not change with increasing concentrations of vancomycin, and maximum killing appears to be achieved once concentrations of 4–5 times the MIC of the pathogen are obtained.

Because the pharmacokinetics of vancomycin involve, at minimum, biexponential decay, further studies attempting to simulate this elimination and any effects on bacterial killing were investigated. Utilizing an in vitro model simulating mono- or biexponential decay, Larrson et al. [9] found no statistically significant difference in either the rate or extent of bacterial killing of *Staphylococcus aureus*. Again, varying concentrations did not induce a change in bactericidal activity, thereby demonstrating that the high drug concentrations achieved during the distribution phase did not enhance the bactericidal activity attained during the elimination phase.

With the understanding that vancomycin killed staphylococci in a concentration-independent fashion, the need to select a pharmacodynamic index that best predicts efficacy was warranted. Duffull et al. [47] used four different vancomycin regimens against *S. aureus* in an in vitro dynamic model.[47] Three dosing schedules with different peak concentrations but the same AUC and a fourth dosing regimen with a smaller AUC were compared for efficacy. The authors found that killing was independent of both peak concentrations and total exposure to drug (AUC). In addition, maintaining a constant concentration above the MIC was equally effective, even with an AUC that was half of that obtained by the other three dosing regimens. This investigation thus supported $T > MIC$ as the optimal parameter for efficacy.

Greenberg and Benes [50] produced time-kill curves from experiments performed in a static environment with 50% bovine serum and constant antibiotic concentrations. They reported a significantly increased rate and extent of killing of *Staphylococcus aureus* when the concentration of vancomycin increased from 20 to 80 mg/L, even though free drug concentrations for all regimens exceeded the MIC by at least three fold. This experiment is one of a few that demonstrated significant concentration-dependent killing with vancomycin alone with concentrations beyond the MIC of the organism.

Vancomycin in combination with other antimicrobials has also been evaluated. Houlihan et al. [51] investigated the pharmacodynamics of vancomycin alone and in combination with gentamicin at various dosing intervals against *Staphylococcus aureus*–infected fibrin-clots in an in vitro dynamic model. Vancomycin monotherapy simulations included continuous infusion, 500 mg every 6 h, 1 g every 12 h, and 2 g every 24 h all of which produced varying peaks and troughs. While all regimens produced concentrations above the MIC for 100% of the dosing intervals, no difference in kill was seen with higher peak concentrations. The investigators also discovered that vancomycin killing was significantly enhanced by the addition of gentamicin whether it was given every 12 or 24 h and, in fact, it killed in a concentration-dependent fashion. The 2 g dosing scheme

5.3 Animal Studies

Animal studies focusing on pharmacodynamic predictors of efficacy for vancomycin are quite limited. Peetermans et al. [10], with a granulocytopenic mouse thigh infection model, showed concentration-dependent killing of staphylococcus for concentrations at or below the MIC. Once concentrations exceeded that value, however, no further kill was seen with increasing doses.

The activity of vancomycin was again evaluated against penicillin-resistant pneumococci using a mouse peritonitis model [55]. In comparing various pharmacokinetic/pharmacodynamic parameters at the ED_{50} values investigators concluded that both $T > MIC$ and Cmax were important predictors of efficacy in their model. These parameters were deemed best predictors because they varied the least. Also, of significance with this study was the discovery that vancomycin activity was not influenced by the penicillin susceptibility of the organism.

Cantoni et al. [56], in an attempt to compare the efficacy of amoxicillin–clavulanic acid against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) versus vancomycin in a rat model of infection, found vancomycin activity to be dependent upon strain. Against the MSSA strain, vancomycin at 30 mg/kg given every 6 h was more effective than the same dose every 12 h. Against the MRSA strain, the four times daily regimen only marginally improved outcome compared to the twice-daily regimen. In that vancomycin concentrations were undetectable after 6 h of therapy, the four times daily regimen was the only therapy that allowed concentrations to remain above the MIC for a majority of the dosing interval. This finding further supports the dependence of vancomycin activity upon the $T > MIC$.

5.4 Human Studies

In vivo, serum bactericidal titers (SBTs) have been evaluated to determine antimicrobial efficacy. An SBT of 1:8 with vancomycin has been associated with clinical cure in patients with staphylococcal infections [57–58]. This SBT was associated with serum concentrations greater than 12 mg/L. James et al. [59] conducted a prospective, randomized, crossover study to compare conventional dosing of vancomycin versus continuous infusions in patients with suspected or documented gram-positive infections. In that the most effective concentration of vancomycin against staphylococcus is not known, the investigators chose a target concentration of 15 μg/mL via continuous infusion and peak and trough concentrations of 25–35 and 5–10 μg/mL, respectively, with conventional dosing of 1 g every 12 h. Despite variability in actual concentrations obtained, continuous infusion produced SBTs of 1:16, whereas conventional dosing produced trough SBTs of 1:8, which was not found to be statistically insignificant. Concentrations remained above the MIC throughout the entire dosing intervals for all patients, whether they received conventional dosing or continuous infusion, and therefore the authors concluded that both methods of intravenous administration demonstrated equivalent pharmacodynamic activities. Although continuous infusion therapy was more likely than conventional dosing to produce SBTs of 1:8 or greater, this study did not attempt to evaluate clinical efficacy associated with such values. Therefore it is unknown, whether improved patient outcome was obtained.

Klepser et al. [60], in a preliminary report of a multicenter study of patients with gram-positive infections receiving vancomycin therapy, found increased rates of bactericidal activity with vancomycin trough concentrations greater than 10 mg/L [60]. Bacterial eradication was also correlated with trough SBTs of 1:8 or greater. Patients that failed therapy had pathogen MICs of >1 mg/L. Hyatt et al. [61] suggest that the area under the inhibitory serum concentration–time curve (AUIC) as well as the organism's MIC were associated with clinical outcome. By performing a retrospective analysis of 84 patients receiving vancomycin therapy for gram-positive infections, these authors found that therapy that produced AUIC <125 and pathogens with MICs >1 mg/L had a higher likelihood of failure. Therefore, these two studies propose that not only $T > MIC$ but also trough values may be important for maximum clinical efficacy.

In summary, vancomycin demonstrates concentration-independent killing of gram-positive bacteria, and peak concentrations do not appear to correlate with rate or extent of kill. Maximum killing is achieved at serum concentrations of 4–5 times the MIC of the infecting pathogen, and sustaining concentrations at or above these levels for the entire dosing interval will likely produce the best antimicrobial effect. Dosing strategies should therefore be aimed at maximizing the time in which concentration at the site of infection remains above the MIC of the pathogen. Whether the most efficient killing is obtained by continuous infusion of vancomycin or by intermittent bolus is controversial. Several studies revealed that no difference in killing is seen between the two methods of administration [51,59,62]; however, such benefits as predictable serum concentrations and ease of administration might be advantageous [62]. Conversely, due to vancomycin's long half-life and the perceived better tolerability associated with intermittent bolus injections, continuous infusion of this drug may not be needed and is often discouraged [62].

6 CLINICAL APPLICATION

6.1 Clinical Uses

Vancomycin is available as vancomycin hydrochloride (Vancocin, Lyphocin, Vancoled, and others) for intravenous use, as powder for oral solution, and as capsules for oral use (Vancocin Pulvules). The indications for vancomycin use

are limited in relation to its strong gram-positive spectrum. Although vancomycin is bactericidal against most gram-positive cocci and bacilli, the intravenous preparation should be reserved for serious gram-positive infections not treatable with β-lactams or other traditional options. The use of vancomycin should not precede therapy with β-lactams for susceptible organisms. Clinical outcomes in both staphylococci and enterococci show vancomycin inferiority as compared to nafcillin and ampicillin regarding bactericidal rate and rapidity of blood sterility [63–67].

Vancomycin is the drug of choice for serious staphylococcal infections that cannot be treated with β-lactams due to bacterial resistance [methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE)] or to the patient's inability to receive these medications [68–70]. Staphylococcal infections include bacteremia, endocarditis, skin and soft tissue infections, pneumonia, and septic arthritis. Dialysis peritonitis due to staphylococci may also be treated with IV vancomycin. Although vancomycin is indicated for *S. aureus* osteomyelitis, bone penetrations are extremely variable, especially between published studies, and treatment with other options could prove more effective [71–75]. Vancomycin is also indicated for infections due to coagulase-negative staphylococci including catheter-associated bacteremia, prosthetic valve endocarditis, vascular graft infections, prosthetic joint infections, central nervous system shunt infections, and other infections associated with indwelling medical devices [68–70]. Complete cure of most medical-device-related infections usually requires the removal of the device due to the biofilm secreted by the *S. epidermidis*. Staphylococcal treatment with vancomycin may require up to 1 week or longer for clinical response in serious infections such as MRSA [70]. Courses of vancomycin that fail to cure serious staphylococcal infections may require the addition of gentamicin, rifampin, or both [69,70,76].

Two significant clinical issues surround the use of vancomycin for the treatment of staphylococcal endocarditis. First, controversy exists as to whether the addition of rifampin is synergistic or antagonistic. Although certain studies have proven the combination to be more efficacious than single therapy with vancomycin [77–79], other more recent publications cite this combination as antagonistic [65]. Additionally, clinical experience with the combination has been inconsistent [80].

The second issue that surrounds vancomycin use for staphylococcal endocarditis is the potentially better outcome with β-lactams. In addition to the in vitro data that suggest that vancomycin is less rapidly bactericidal than nafcillin, clinical data exist to support this conclusion [63–67]. Although no large-scale comparison studies exist to evaluate the efficacy of vancomycin versus β-lactams in staphylococcal endocarditis, assumptions can be formulated from published studies. In a study by Korzeniowski and Sande [67], the duration of bacteremia due to *S. aureus* endocarditis lasted a median of 3.4 days after treatment with

nafcillin, whereas bacteremia lasted a median of 7 days for patients treated with vancomycin in a study conducted by Levine et al. [65]. The patients in the Levine study were infected with methicillin-resistant *S. aureus* in comparison to the methicillin-sensitive organisms from the Korzeniowski study, yet, in general, the morbidity and mortality of bacteremic infections due to MSSA and MRSA are comparable [66]. In a small study that compared vancomycin to nafcillin in *S. aureus* endocarditis, the investigators found that patients treated with nafcillin plus tobramycin had a cure rate of 94%, whereas only 33% of patients treated with vancomycin plus tobramycin were cured [64]. Worth mentioning, however, is the fact that while the nafcillin plus tobramycin group consisted of 50 patients, only three patients received vancomycin plus tobramycin due to β-lactam allergy. Small and Chambers [63] performed another study that evaluated the use of vancomycin in 13 patients with staphylococcal endocarditis, five of whom failed therapy. The reason for vancomycin ineffectiveness in these cases may be the need for prolonged high levels of a bactericidal antibiotic, however, with longer durations of bacteremia and poorer clinical outcomes, serious consideration needs to be given to whether vancomycin should be considered at all in patients with MSSA endocarditis who can tolerate β-lactam therapy.

Streptococcal infections not treatable with β-lactams or other traditional options are also proper indications for vancomycin [68–70]. Endocarditis due to β-lactam-resistant *S. viridans* or *S. bovis* is a common use of vancomycin, although organisms with elevated MIC values may require that it be combined with an aminoglycoside. Vancomycin is the drug of choice for pneumococcal infections showing high-level resistance to penicillin [68–70]. Cefotaxime or ceftriaxone plus rifampin may be needed to adequately cover *S. pneumoniae* meningitis due to vancomycin's poor penetration in the central nervous system [81–82]. Although penetration is enhanced while meninges are inflamed, as in meningitis and shunt infections, certain cases may require intrathecal or intraventricular administration to obtain therapeutic levels.

As for enterococcal infections, vancomycin represents the treatment of choice for ampicillin-resistant enterococcus [68–70]. Enterococcus endocarditis and other infections may require the addition of an aminoglycoside, such as gentamicin. Vancomycin is also the treatment of choice for corynebacterial infections [68–70].

Empirically, vancomycin should be used only in limited situations. Vancomycin can be considered for febrile neutropenic patients presenting with clinical signs and symptoms of gram-positive infections in areas of high MRSA prevalence [39]. Other indications for empirical use of vancomycin in neutropenic patients with fever include the presence of severe mucositis, colonization with MRSA or penicillin-resistant *Streptococcus pneumoniae*, prophylaxis with quinolone antibiotics, or obvious catheter-related infection [83]. Vancomycin should be discontinued after 4–5 days if no infection is identified or if initial cultures

for gram-positive organisms are negative after 24–48 h. For prophylaxis, vancomycin may be used perioperatively with prosthesis implantation only in severely β-lactam allergic patients [39]. Vancomycin is also used for endocarditis prophylaxis for β-lactam allergic patients.

Orally, vancomycin is indicated for metronidazole-refractory antibiotic-associated colitis caused by *Clostridium difficile* [39,68–70]. Intravenous administration of vancomycin typically does not achieve adequate levels in the colon lumen to successfully treat antibiotic-associated colitis; however, there are rare reports of success with this route cited in the literature.[39] Administration via nasogastric tube, enema, ileostomy, colostomy, or rectal catheter may be needed if the patient presents with severe ileus. Oral vancomycin has also been used prophylactically to prevent endogenous infections in cancer and leukemia patients. This regimen seems to decrease the *C. difficile* associated with the chemotherapy [85–87].

6.2 Inappropriate Uses

Although vancomycin is an effective option for most gram-positive infections, the drug needs to be judiciously used to prevent the emergence and spread of resistance. Vancomycin should not be used when other drug options such as β-lactams are viable. Microbial susceptibilities need to be treated to determine the appropriateness of vancomycin therapy, and the antibiotic should be changed if the organism is susceptible to a different agent.

The CDC has published guidelines for the appropriate use of vancomycin (Tables 1 and Table 2) [39]; however, vancomycin misuse around the nation is widespread. A retrospective study from May 1993 to April 1994 identified 61% of vancomycin usage as inappropriate according to the CDC criteria [88]. A similar evaluation published in 1997 found that only 47% of vancomycin orders prescribed for 7147 patients were appropriate [89]. According to this study, inade-

Table 1 Appropriate Use of Vancomycin

Treatment of serious infections due to β-lactam-resistant gram-positive pathogens
Treatment of gram-positive infections in patients with serious β-lactam allergies
Antibiotic-associated colitis failure to metronidazole
Endocarditis prophylaxis per American Heart Association recommendations
Antibiotic prophylaxis for implantation of prosthetic devices at institutions with a high rate of infections due to methicillin-resistant staphylococci

Source: Ref. 37.

Table 2 Inappropriate Use of Vancomycin

Routine surgical prophylaxis
Empirical treatment for febrile neutropenic patients without strong evidence of gram-positive infection and high prevalence of β-lactam resistant organisms in the institution
Treatment in response to a single positive blood culture for coagulase-negative staphylococci when other blood cultures taken appropriately in the same time frame are negative
Continued empirical use without positive culture for β-lactam-resistant gram-positive pathogen
Systemic or local prophylaxis for central or peripheral catheter
Selective gut decontamination
Eradication of methicillin-resistant *Staphylococcus aureus* colonization
Primary treatment of antibiotic-associated colitis
Routine prophylaxis for patients on chronic ambulatory peritoneal dialysis
Routine prophylaxis for very low birthweight infants
Topical application or irrigation

Source: Ref. 37.

quate use and inappropriate control patterns were similar whether large teaching centers or small rural hospitals were evaluated. As such, alternative methods of vancomycin control need to be implemented to ensure adequate use and limit resistance.

6.3 Toxicity and Adverse Drug Reactions

A variety of adverse reactions have been associated with vancomycin, including fever, rash, phlebitis, neutropenia, nephrotoxicity, auditory toxicity, interstitial nephritis, and infusion-related reactions. Many of the infusion-related reactions were likely due to impurities in the initial formulations and have been significantly reduced with the newer formulations. The red man or red neck syndrome is an anaphylactoid reaction related to rapid infusion of large doses, typically >12 mg/(kg · h) [13,69–70]. The reaction begins 10 min after infusion and generally resolves within 15–20 min after stopping the dose. Patients may experience tachycardia, chest pain, dyspnea, urticaria, and swelling of the face, lips, and eyelids. Additionally, patients may experience a hypotensive episode with a 25–50% reduction in systolic blood pressure. Interestingly, volunteers receiving vancomycin infusions have a higher propensity toward the reaction than patients [62]. The reason is unknown. Symptoms of red man syndrome appear to be histamine-mediated; however, investigations are inconclusive. Extending the administration of vancomycin to 1 h or a maximum of 15 mg/min should prevent most infusion-related reactions.

Vancomycin toxicity was retrospectively studied by Farber and Moellering [90] in 98 patients. They noted a 13% incidence of phlebitis, a 3% incidence of fever and rash, and a 2% incidence of neutropenia. However, this report may overestimate true adverse reactions because of the inclusion of many potentially high-risk patients. Interestingly, whereas other studies have shown that concomitant aminoglycosides are not a risk factor for nephrotoxicity [91], patients receiving both vancomycin and an aminoglycoside experienced a 35% incidence of reversible nephrotoxicity, which is more than expected from either antibiotic alone. Only 5% of patients receiving vancomycin alone experienced nephrotoxicity. The authors also found that patients with nephrotoxicity had trough concentrations of 20–30 mg/L.

Vancomycin ototoxicity has been reported with peak serum concentrations of 80–100 mg/L [92]. Geraci [92] identified two patients with vancomycin-induced ototoxicity, one of whom had a history of renal disease, an elevated blood urea nitrogen on admission, and a recorded diastolic blood pressure of zero. Serum concentrations determined 3–6 h after the dose was administered ranged from 80 to 95 mg/L. Due to the biexponential nature of the vancomycin serum concentration–time curve, the true vancomycin peak was likely near 200–300 mg/L. Farber and Moellering [90] also reported the occurrence of ototoxicity in a patient who, at 1 h postinfusion, had serum concentrations of <50 mg/L; however, the true peak was likely in the toxic range as defined by Geraci [92].

In summary, the incidence of adverse reactions associated with vancomycin are relatively infrequent. Only approximately 40 cases of oto- and nephrotoxicity were reported in the medical literature in the years 1956–1984 despite incessant use. Most of these cases were complicated by concomitant aminoglycoside therapy and pre-existing renal problems, as well as investigator discrepancies in interpreting serum levels.

6.4 Dosing and Therapeutic Monitoring

Medical literature abounds that questions the need to therapeutically monitor vancomycin concentrations. Cantu et al. [93] suggest that monitoring vancomycin concentrations is unnecessary in that no correlation has been demonstrated between drug levels, toxicity, and clinical response. Opponents propose that vancomycin can be dosed using published nomograms based on the the patient's age, weight, and estimated creatinine clearance. Conversely, Moellering et al. [94] argue that therapeutic vancomycin monitoring would in fact be prudent for optimal clinical response and restriction of toxicity in such situations as patients on hemodialysis, patients with rapidly changing renal function, and patients receiving high dose vancomycin or concomitant aminoglycoside therapy.

Numerous strategies do exist for empirically dosing vancomycin. Administering 500 mg every 6 h, 1 g every 12 h, or 20–40 mg/kg body weight/day are commonly employed. In addition, nomograms exist such as those established by Matzke et al. [95], Moellering et al. [94], Lake and Peterson [96], and Nielsen et al. [97]. Serious faults lie in the dependence of these nomograms on efficacious use of vancomycin, however, because the authors assume rather than prove that their method of pharmacokinetically modeling the data was appropriate. Most empirical regimens were designed to provide peak concentrations of 20–40 mg/L and trough concentrations of 5–10 mg/L (or approximately 5 times the MIC of the infecting pathogen), however, such practices place only 3–23% of patients in this therapeutic range, according to one published study [98]. Unfortunately, although such goals in serum levels are set, no solid data are available to support this therapeutic range and accordingly, serum peak and trough concentrations have been selected somewhat arbitrarily, based on speculations from retrospective studies, case reports, and personal opinions. Peak concentrations appear to play little to no role in the efficacy of the drug and appear to have limited involvement in toxicity unless exceedingly large peak values are obtained. On the other hand, trough concentrations may be useful monitoring parameters. Because vancomycin is a concentration-independent killer, the goal of therapy should be to maintain the unbound concentration above the microbial MIC for a significant portion of the dosing interval because regrowth of most organisms will begin shortly after drug concentrations fall below the MIC. A depiction of predicted vancomycin pharmacodynamic indices obtained from a typical intravenous dose using various pathogen MICs is presented in Table 3.

The role of vancomycin degradation products also needs to be considered when interpreting levels in patients with renal failure where half-lives are significantly extended [99–100]. In vitro and in vivo, vancomycin breaks down over time to form crystalline degradation products. Antibodies in commercial assays, such as TDx fluorescence polarization immunoassay, cross react with major and

Table 3 Estimated Vancomycin Pharmacodynamic Ratios for Various MIC Values[a]

MIC (mg/L)	C_{ss}/MIC	$T > MIC$ (h)	AUC_{24}/MIC
0.25	140	12	784
0.5	70	12	392
1.0	35	12	196
2.0	17.5	12	98
4.0	8.75	12	49
8.0	4.38	11	24.5

[a] Calculations based on a 1 g dose given every 12 h to a 70 kg patient with normal renal function.

minor degradation products thereby overstating factor B (active drug) content in the level. This can result in an overstated vancomycin concentration of 20–50%.

In summary, trough concentrations of 5–10 mg/L appear to be reasonable goals for vancomycin therapy in that MICs of most gram-positive pathogens are ≤1 mg/L. Such concentrations would allow the unbound concentrations to remain above the MIC of the organism for the entire dosing interval. Administering 10–15 mg/kg per dose and adjusting the dosing interval per renal function based upon numerous published nomograms is not likely to produce "toxic" peak concentrations and should allow "therapeutic" concentrations throughout the dosing interval in the majority of patients with normal renal function. Loading doses are not typically needed, because transiently high distribution phase concentrations are unlikely to enhance bacterial killing. However, loading doses may be reasonable in patients in whom the site of infection is distal to the central compartment or poorly accessible. Until a relationship among clinical efficacy, toxicity, and vancomycin concentration is established, vancomycin therapy will inevitably continue to be monitored in an attempt to improve patient outcome. Whether therapeutic monitoring of vancomycin should be a standard of practice or is necessary only in patients receiving high dose therapy, patients on concomitant aminoglycoside therapy, or patients with renal insufficiency or failure on dialysis is likely to remain a personal preference until further studies establish guidelines. However, if the CDC guidelines for appropriate vancomycin usage were stringently followed, at least half of vancomycin use could be eliminated, leaving the remaining patients to be monitored.

7. OTHER GLYCOPEPTIDES

7.1 Teicoplanin

Teicoplanin, like vancomycin, binds to the terminal D-alanyl-D-alanine portion of the peptidoglycan cell wall of actively growing gram-positive bacteria to exert its bactericidal activity [101]. Currently available only in Europe, teicoplanin can be used to treat infections caused by both methicillin-sensitive and -resistant strains of *Staphylococcus aureus*, *S. epidermidis*, streptococci, and enterococci. Clinical trials have demonstrated teicoplanin to be a safe, well tolerated agent, with reports of side effects occurring in 6–13% of recipients [101]. The most prevalent adverse reactions reported are pain at the injection site and skin rash. Nephro- and ototoxicity are uncommon even when the drug is used concomitantly with other nephro- and ototoxic drugs. Pharmacokinetically, teicoplanin differs from vancomycin. The half-life is considerably longer (~47 h) and the percent protein-bound nears 90% [101]. Also, teicoplanin can be administered by either the intravenous or intramuscular route as opposed to vancomycin, which is limited parenterally to the intravenous route. Pharmacodynamic evaluations virtually

duplicate those of vancomycin once the heightened protein binding of teicoplanin and subsequent lower active free concentrations are accounted for [102]. Further reviews of teicoplanin can be found elsewhere [101,103].

7.2 LY333328

LY333328 (Eli Lilly and Company) is a synthetic glycopeptide that is currently being developed to treat gram-positive bacterial infections, including those resistant to vancomycin. Because it is still in the early stages of development, little is known about the antibiotic. The drug acts on the same molecular target as vancomycin and other glycopeptide antibiotics [104]; however, LY333328 appears to display concentration-dependent bactericidal activity against gram-positive pathogens [102–106]. The half-life is long, approaching 10.5 days, which may allow for infrequent dosing [107]. Pharmacodynamic investigations and clinical efficacy trials are needed prior to drug approval and utilization.

8. CONCLUSION

With years of clinical experience, vancomycin has proven to be a safe and efficacious agent against gram-positive pathogens, including many multidrug-resistant strains. Despite this history, to date the therapeutic range has not been rigorously defined, however, going beyond the currently suggested therapeutic range is not likely to improve antibiotic performance. The accumulation of in vitro and in vivo studies suggests that vancomycin is a concentration-independent killer of gram-positive organisms with maximum killing occurring at serum concentrations of 4–5 times the MIC of the infecting organism. High peak concentrations are not associated with an improved rate or extent of kill, and therefore therapy should be targeted toward sustaining serum concentrations above the MIC for a large portion of the dosing interval. With the high level of vancomycin use, the development and spread of vancomycin-resistant organisms is a formidable and predictable occurrence. At a time when we are attempting to be more prudent and judicious in the use of vancomycin, we also find ourselves more dependent on the drug. Unfortunately, this combination of factors may drive bacterial resistance and ultimately nullify a drug that has been a gold standard product for a half a century.

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9

Macrolide, Azalide, and Ketolide Pharmacodynamics

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1 INTRODUCTION

The macrolides and azalides have activity against gram-positive bacteria and are relatively weakly active against many gram-negative bacteria. These agents also penetrate well into mammalian tissue and achieve high concentrations in mammalian cells and are therefore very useful in the treatment of infections caused by intracellular pathogens. Their spectrum of activity makes them a good choice for the treatment of community acquired respiratory tract infections, because the organisms associated with such diseases usually involve *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* and frequently involve intracellular organisms (Table 1) [1–3]. The macrolides and azalides (either as the parent compound or in combination with a microbiologically active metabolite) have adequate activity against these pathogens and have emerged as useful and popular agents for the treatment of milder forms of these diseases.

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Preface

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